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Short- and long-term survival after ST-elevation myocardial infarction treated with pharmacoinvasive versus primary percutaneous coronary intervention strategy: a prospective cohort study

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ABSTRACT

Objective Compare survival in patients with ST-elevation myocardial infarction (STEMI) treated with a pharmacoinvasive (PI) or primary percutaneous coronary intervention (pPCI) strategy based on estimated time to PCI.

Design Prospective observational cohort study. Consecutive STEMI patients were registered on admission to our PCI centre and classified in a PI or pPCI group, based on the reperfusion strategy chosen in the prehospital or local hospital location. Time and cause of death was provided by the Norwegian Cause of Death registry. Mortality at 30 days, Kaplan-Meier survival and incidence of cardiovascular (CV) death was estimated. Adjusted effect of PI versus pPCI strategy on survival was estimated using logistic and Cox regression and propensity score weighting.

Setting Single-centre registry in Norway during 2005–2011, within a regional STEMI network allocating patients to a PI strategy if estimated time to PCI >120 min.

Primary outcomes 30-day mortality and survival during follow-up.

Secondary outcome Incidence of CV death during follow-up.

Results 4061 STEMI patients <80 years were included, 527 (13%) treated with a PI strategy and 3534 (87%) with a pPCI strategy. Median symptom-to-needle time was 110 min (25–75th percentile 75–163) in the PI group vs symptom-to-balloon 230 min (149–435) in the pPCI group. 30-day mortality was 3.2% and 5.0% in the PI and pPCI groups ($OR_{adjusted}$0.58 (95% CI 0.30 to 1.13)) and 8-year survival was 85.9% (95% CI 80.9% to 89.6%) and 79.3% (95% CI 76.9% to 81.6%), respectively ($HR_{adjusted}$ 0.72 (95% CI 0.53 to 0.99)). Unadjusted incidence of 8-year CV death was 7.0% (95% CI 4.4% to 10.4%) in the PI group vs 12.4% (95% CI 9.9% to 15.2%) in the pPCI group. Adjusted long-term CV death was also lower in the PI group.

Conclusion STEMI patients treated with a PI strategy experienced better survival compared with a pPCI strategy, also when adjusting for baseline characteristics. This supports using a PI strategy for eligible STEMI patients when pPCI cannot be performed within 120 min.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Well-described prospectively collected data for a large clinical ST-elevation myocardial infarction (STEMI) cohort with complete long-term follow-up, yielding a high internal validity.
⇒ Outcomes reflecting treatment within an established regional STEMI network, allocating patients to the most efficient reperfusion strategy based on geographical distance and transfer delays to pPCI.
⇒ The observational study design may imply selection bias and unmeasured confounding, thus causality may not be claimed.
⇒ The external validity of results may be limited, and inference of results should be made with caution and for similar STEMI cohorts.

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is the recommended reperfusion strategy for patients with ST-segment elevation myocardial infarction (STEMI), if delivered within 120 min from diagnosis at an experienced centre with a 24/7 pPCI service.[1 2] In geographical areas with >120 min expected time delay to pPCI, a pharmacoinvasive (PI) strategy (ie, fibrinolysis on place followed by immediate transportation to a PCI capable hospital for rescue PCI in case of failed fibrinolysis, and otherwise routine coronary angiography within 2–24 hours) is recommended within 12 hours from symptom onset, for patients without contraindications.[1]

The mortality benefit of reperfusion therapy in STEMI is time-dependent,[3 4] and registry data have indicated that pPCI loses its advantage over fibrinolysis if the PCI-related delay is >120 min.[5] Some observational studies even suggest that STEMI patients treated with a PI strategy have better survival compared with late pPCI.[6–8] Although pPCI capacity is increasing in Europe and other

parts of the world,[9–13] a significant proportion of STEMI patients do not receive timely reperfusion as recommended.[14 15] Therefore, data are needed on outcomes within established STEMI networks allocating patients to a PI or pPCI strategy based on geographical distance and expected time delays to pPCI. We used data from the local MI registry at Oslo University Hospital (OUH) Ulleval, and aimed to compare 30-day mortality, long-term survival and cardiovascular (CV) death in patients <80 years treated with a PI vs pPCI strategy within such a regional STEMI network.

METHODS

Study design

This was a prospective, observational cohort study, investigating the effect of a PI vs pPCI strategy for hospital admitted STEMI patients.

Study population and system of care

OUH is the regional cardiac invasive centre for a population of about 1 400 000 in South-Eastern Norway. A certain proportion of the patients live 100–400 km away. A well-established STEMI network exists where a prehospital ECG is taken by the ambulance on arrival in a symptomatic patient. The ECG is sent by telemedicine to the nearest hospital (ie, local hospital or pPCI centre) for evaluation by a dedicated physician (cardiologist or attending resident). Occasionally, the patient would present directly at the local hospital with symptoms, and the diagnostic ECG was taken there. If STEMI was diagnosed by the responsible physican at the local hospital, and expected transfer delay to the pPCI centre was ≥90 min, the local protocol recommended treatment with fibrinolysis if there were no contraindications, in addition to aspirin, clopidogrel and low-molecular weight heparin. Before 2010, patients receiving fibrinolysis were transferred to our cardiac invasive centre according to an ischaemia-guided strategy. After 2010, routines were changed to implement a PI strategy, that is, fibrinolysis with immediate transfer to our cardiac invasive centre with rescue PCI in case of failed fibrinolysis, or subsequently early routine angiography within 2–24 hours.[16]

The Ulleval MI registry was a local quality registry, with prospective recording of consecutive MI patients ≥18 years admitted to OUH Ulleval between 1 September 2005 and 31 December 2011. The inclusion of patients ended due to the establishment of a nationwide MI registry. The AMI diagnosis was based on current international criteria,[17 18] and categorised as STEMI or non-STEMI (NSTEMI) based on the index ECG. Troponin T was used as the primary biochemical marker. In this study, only STEMI patients were included. Each patient was only included with the first STEMI admission during the study period. The treatment strategy had already been defined at the time of diagnosis by the physician interpreting the first ECG. Patients in the PI group had received prehospital fibrinolysis or fibrinolysis at the local hospital, before transportation to OUH Ulleval for rescue or routine coronary angiography and PCI, if indicated. Patients in the pPCI group were transported directly to OUH Ulleval and underwent immediate coronary angiography and primary PCI if indicated. Patients were included in the study at the time of hospital admission. Patients who died during transportation were not registered.

Exclusion criteria were age ≥80 years, in-hospital or procedure-related STEMI, or lack of a defined reperfusion strategy (figure 1).

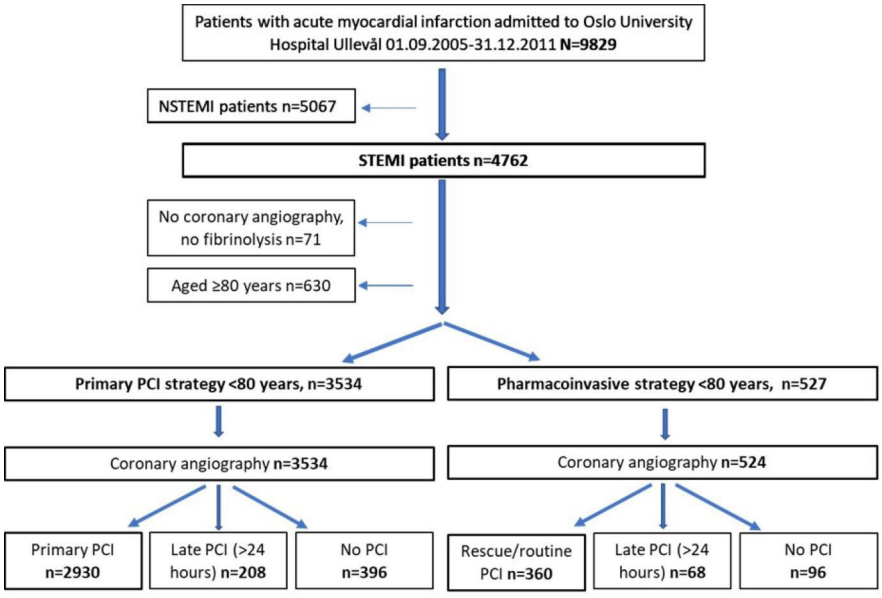

Figure 1 Study population flow chart. NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

Study variables and in-hospital treatment

Definitions of variables and routines for data quality assurance in the Ulleval MI registry have been described elsewhere.[19 20] Prehospital resuscitation was defined as cardiac arrest with cardiopulmonary resuscitation before admission. Time to reperfusion was defined as time from symptom-to-needle for patients treated with a PI strategy, and symptom-to-balloon for patients treated with pPCI. Time of diagnosis was not registered. Level of serum-creatinine (µmol/L) was measured at the time of admission, as a proxy for baseline renal function. The smoking variable included current or previous smokers, with 8.9% missing values. All other variables included in the multivariate analyses had >97% non-missing values.

In general, a coronary stenosis obstructing >50% of the lumen was considered significant. Multiple vessel disease was defined as stenosis in ≥2 coronary arteries or in the left main stem. The decision to perform PCI was made by the treating physicians. All patients received standard of care medications according to STEMI guidelines,[21] at the discretion of the treating physician.

Outcomes

The primary outcomes were 30-day mortality and survival during follow-up. The secondary outcome was incidence of CV death during follow-up. Survival data were obtained by linkage with the Norwegian Cause of Death Registry, containing vital status, time of death and cause of death classified as CV-cause, cancer-cause or other cause-death, throughout 2013. Follow-up time varied for each patient due to the dynamic inclusion period. Time zero was the time of admission to OUH Ulleval. Patients were censored if they were alive at the closing date 31 December 2013.

Statistical analysis

Categorical variables are reported as frequencies and percentages of non-missing values, and continuous variables as mean (SD) or median (25–75th percentile). Differences between the PI and pPCI strategy groups were compared using χ^2 or Fisher's exact test for categorical data, and Student's t-test or Mann-Whitney U test for continuous data. OR for 30-day mortality for the PI versus pPCI strategy was calculated using logistic regression in three models: (1) Crude (unadjusted), (1) age adjusted and (1) multivariable adjusted (age, female gender, smoking, previous hypertension, diabetes mellitus, MI, angina pectoris, cerebrovascular stroke and peripheral artery disease, prehospital resuscitation and serum-creatinine level at admission). Cumulative survival was estimated with the Kaplan-Meier method and difference between groups tested with the log-rank test. Cox regression was used to calculate the HR for overall long-term mortality risk in the PI versus pPCI group in three models: (2) crude, (2) age adjusted and (2) multivariable adjusted (same variables as in the logistic regression model 1). The PI strategy was considered as the treatment (exposure) variable in all adjusted analyses. The proportional hazards assumption was evaluated with the log-log survival functions against time. Prespecified analyses of effect modification by age, gender and time from symptom onset to reperfusion (symptom-to-needle or symptom-to-balloon) on the treatment–outcome association were performed by stratification and including an interaction term into the multivariable Cox regression model, one at a time.

When examining the incidence of CV death during follow-up, death from cancer or other causes may occur as competing risks.[22] To handle this issue, we estimated the cumulative incidence function (CIF) for CV death in the PI versus pPCI groups, taking competing risk into account.[23] The competing risk analysis was repeated with adjustment for baseline characteristics using propensity score (PS) weighting, as described below.

The PS is the probability of being treated (ie, with a PI strategy), conditional on observed baseline characteristics. The PS weights are used to create a sample where the distribution of observed baseline characteristics will be similar between treated (ie, PI strategy) and untreated (ie, pPCI strategy) patients.[24] Under certain assumptions, most importantly that there are no residual confounding, PS weights aim to identify the marginal difference in outcome one would have seen if all patients were treated with a PI strategy versus where all were treated with a pPCI strategy. The fact that PS weighting identify marginal estimates, also makes it a convenient approach for estimating groupwise adjusted survival and cumulative incidence curves.[25] In our study, the PS was calculated using a logistic regression model with PI-strategy (yes or no) as dependent variable, given the measured covariates known at baseline (same as in the multivariate regression models 1 and 2 described above).[24 26] For each patient within the study sample, a weight was assigned based on the inverse of the probability of receiving the patient's actual treatment.[27] PS weighting may result in increased variance and thus a higher degree of uncertainty than regression analyses, even with well-balanced covariates between the two treatment groups.[28] Stabilised weights were used to address the issue of inaccurate weights in case of patients with a very low probability of being treated. Robust variance estimation was used to account for the sample weights.[24] A balance check of the distribution of baseline covariates in propensity weighted treatment groups was satisfactory with a standardised difference <0.1.[27 29] PS-weighted Kaplan-Meier survival curves and PS-weighted CIFs were computed, and differences between the PI and pPCI groups were compared using weighted Cox regression and Fine and Gray competing risks regression, respectively.[23]

A two-sided p<0.05 was considered significant. Analyses performed with STATA/IC V.16.1. (StataCorp). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Patient and public involvement

No patients involved.

Table 1 Baseline characteristics

	Pharmacoinvasive strategy n=527	Primary PCI strategy n=3534	P value
Age, years*	59.6 (10.1)	60.4 (10.8)	0.068
Female, n (%)	103 (19.5)	728 (20.6)	0.575
Current or previous smoker, n (%)	376 (76.1)	2304 (70.4)	0.003
Previous hypertension, n (%)	169 (32.1)	1144 (32.4)	0.890
Diabetes mellitus, n (%)	49 (9.3)	455 (12.9)	0.020
Angina pectoris n (%)	27 (5.1)	244 (6.9)	0.127
Previous myocardial infarction, n (%)	49 (9.3)	373 (10.6)	0.378
Previous stroke, n (%)	16 (3.1)	152 (4.3)	0.174
Peripheral artery disease, n (%)	16 (3.1)	118 (3.4)	0.717
Serum creatinine at admission, µmol/l†	73 (63–84)	73 (62–86)	0.497
Prehospital resuscitation, n (%)	43 (8.2)	219 (6.2)	0.087

STEMI patients aged <80 years admitted to Oslo University Hospital Ulleval 2005–2011, N=4061.
*Mean (SD).
†Median (25–75th percentile). Missing values <2% unless stated otherwise.
PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

RESULTS

Study population and baseline characteristics

A total of 4762 STEMI patients were registered between 1 September 2005 and 31 December 2011 (figure 1). Patients who did not receive any reperfusion treatment (neither fibrinolysis nor coronary angiography, n=71) and patients ≥80 years (n=16 in the PI group (2.9%) and n=510 in the pPCI group (12.6%)) were excluded. A PI strategy was applied in 527 patients (13.0%), and a pPCI strategy in 3534 patients (87.0%). Baseline characteristics are shown in table 1.

In the subgroup which did not receive any reperfusion therapy (71 patients), patients were older, with a higher proportion of women, baseline risk factors and in-hospital complications, compared with patients in the PI and pPCI groups. In-hospital mortality for STEMI patients<80 years without reperfusion therapy was 45.1% (data not shown).

Treatment and short-term mortality

Table 2 presents reperfusion treatment, in-hospital measurements, procedures and complications. Time to attempted reperfusion was shorter in the PI group compared with the pPCI group (table 2). The median PCI-related delay was 120 min. In the pPCI strategy group, PCI was actually performed in 3138 patients (88.8%), 166 (4.7%) were referred to coronary artery bypass grafting and 230 (6.5%) received angiography only (table 2). Use of in-hospital medications are presented in online supplemental table S1.

Overall, 30-day mortality was 3.2% in the PI group and 5.0% in the pPCI group (OR 0.63, 95% CI 0.37 to 1.03, table 3). After adjustment for age and baseline risk factors, the risk of 30-day mortality was 42% lower in the PI vs pPCI group (p=0.110, table 3).

Long-term survival and CV mortality during follow-up

Follow-up time was median 4.7 years (3.0–6.3) and maximum 8.3 years. Kaplan-Meier survival plots are shown in figure 2. The incidence rate of mortality during follow-up was 0.021 per person-year in the PI group versus 0.031 per person-year in the pPCI group. Annual survival rates are shown in online supplemental table S2. The 8-year cumulative survival was 85.9% (95% CI 80.9% to 89.6%) for patients in the PI group and 79.3% (95% CI 76.9% to 81.6%) in the pPCI group (crude HR 0.68 (95% CI 0.52 to 0.90), table 4).

After multivariate adjustment, 8-year mortality risk was 28% lower for patients treated with a PI versus pPCI strategy (table 4). The multivariate Cox model was stratified on prehospital resuscitation status (yes/no), due to violation of the PH-assumption. Cox regression models with multivariate adjustment in model 1 and 2 were repeated without the smoking-variable, with no significant change in adjusted hazards (data not shown). Better adjusted long-term survival for the PI strategy group was also found using the PS weighted Kaplan-Meier estimator, although not statistically significant (figure 3). Standardised differences for balance of baseline covariates before and after PS weighting were satisfactory (online supplemental table S3). A 8-year incidence of CV death was 7.0% in the PI group vs 12.4% in the pPCI group (figure 4). The lower cumulative incidence of CV death in the PI versus pPCI group persisted after adjustment using PS weighting (online supplemental figure S1). The competing risk analysis demonstrated that the lower incidence of CV death in the PI group was not due to increased incidence of cancer or other-cause deaths during follow-up (online supplemental figure S1).

Table 2 Reperfusion treatment, in-hospital procedures, complications and short-term mortality

	Pharmacoinvasive strategy n=527	Primary PCI strategy n=3534	P value
Fibrinolysis, n (%)	527 (100)	–	
Prehospital fibrinolysis, n (%)	189 (35.9)	–	
Local-hospital fibrinolysis, n (%)	326 (61.8)	–	
Coronary angiography, n (%)	524 (99.4)	3534 (100)	<0.001
Coronary angiography, no PCI, n (%)	96 (18.2)	396 (11.2)	<0.001
PCI, n (%)	428 (81.2)	3138 (88.8)	<0.001
Primary PCI, n (%)	–	2930 (82.9)	
Rescue/routine early PCI, n (%)	360 (68.3)	–	
Late (>24 hours) PCI, n (%)	68 (12.9)	208 (5.9)	<0.001
Symptom-to-fibrinolysis, minutes*	110 (75-163)†	–	
Symptom-to-admission, minutes*	314 (230–525)	192 (110–420)	<0.001
Symptom-to-balloon, minutes*	351 (272–621)	225 (147–420)	<0.001
Fibrinolysis-to-balloon, minutes*	212 (165–341)	–	
Door-to-balloon time, minutes*	37 (30–64)	35 (28–50)	<0.001
Maximum troponin T, µg/*L	4.60 (1.63–8.88)‡	3.70 (1.51–7.50)	0.004
Multiple vessel disease, n (%)	260 (49.7)	1763 (50.0)	0.814
CABG, n (%)§	33 (6.3)	166 (4.7)	0.121
IABP, n (%)	22 (4.2)	227 (6.4)	0.045
Invasive ventilation, n (%)	21 (4.0)	182 (5.2)	0.253
Pacemaker or ICD, n (%)	6 (1.1)	75 (2.1)	0.132
Cardiogenic shock, n (%)	14 (2.7)	154 (4.4)	0.067
Heart failure, n (%)	58 (11.0)	325 (9.2)	0.185
Major bleed, n (%)	10 (1.9)¶	47 (1.3)**	0.303
Cerebrovascular stroke, n (%)	3 (0.6)	15 (0.4)	0.839
Intracerebral haemorrhage	1 (0.2)	1 (0)	–
Re-infarction, n (%)	3 (0.6)††	38 (1.1)**	0.404
Mortality			
In-hospital mortality, n (%)	14 (2.7)	128 (3.6)	0.261
30-day mortality, n (%)	17 (3.2)	177 (5.0)	0.074
30-day CV mortality, n (%)	15 (2.9)	163 (4.6)	0.065

Missing ≤3% if not stated otherwise.
STEMI patients aged <80 years, N=4061.
*Median (25–75th percentile).
†Missing 12%.
‡Missing 5%.
§Operated or transferred for operation.
¶Missing 19%.
**Missing 18%.
††Missing 15%.
CABG, coronary artery bypass grafting; CV, cardiovascular; IABP, intra-aortic balloon pump; ICD, implantable cardiac defibrillator; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

DISCUSSION

In this clinical cohort study of 4061 STEMI patients <80 years treated in a regional STEMI network, where 13% were treated with a PI strategy and 87% with a pPCI strategy, we found that (1) Crude 30-day mortality was 3.2% in the PI group vs 5.0% in the pPCI group, with 42% lower risk in the PI group after multivariable adjustment, although not statistically significant. (2) Crude 8-year survival was 85.9% in the PI group and 79.3% in the pPCI group, with 28% lower mortality risk in the PI group after multivariable adjustment. (3) The PI strategy was associated with lower incidence of CV death during 8 years of follow-up compared with the pPCI strategy (7.0% vs 12.4%, respectively).

Table 3 Logistic regression analysis, 30-day mortality

	Pharmacoinvasive versus primary PCI strategy OR (95% CI)
30-day all-cause mortality	
Crude	0.63 (0.37 to 1.03)
Age adjusted	0.66 (0.40 to 1.10)
Multivariate adjusted*	0.58 (0.30 to 1.13)

*Covariates: age, gender, smoker or ex-smoker, previous hypertension, diabetes mellitus, angina pectoris, myocardial infarction, stroke or peripheral artery disease, prehospital resuscitation, serum creatinine.
PCI, percutaneous coronary intervention.

Table 4 Cox regression, all-cause death during follow-up

	Pharmacoinvasive versus primary PCI strategy HR (95% CI)
All-cause mortality	
Crude	0.68 (0.52 to 0.90)
Age adjusted	0.71 (0.54 to 0.94)
Multivariate adjusted*	0.71 (0.52 to 0.97)†
Stratified on prehospital resuscitation, yes/no*	0.72 (0.53 to 0.99)

*Covariates: age, female gender, previous- or current smoker, previous hypertension, diabetes mellitus, angina pectoris, myocardial infarction, stroke or peripheral artery disease, prehospital resuscitation, serum-creatinine
†Proportional hazards assumption not fulfilled. Median follow-up: 4.7 years (25–75th percentile: 3.0–6.3).
PCI, percutaneous coronary intervention.

Our findings of 3.2% and 5.0% 30-day mortality in the PI and pPCI groups, respectively, correspond with previous data suggesting 4–6% short-term mortality after STEMI.[2 14 30 31] However, STEMI patients that are elderly, with a high prevalence of CV risk factors or with complications such as cardiac arrest, cardiogenic shock and heart failure, may experience a 30-day mortality of up to 45%, as we also describe for the patients without reperfusion therapy.[20 32 33] Crude long-term survival was markedly better in the PI compared with the pPCI group, with 28% lower risk after multivariable adjustment using the Cox regression model. Lower long-term risk for the PI group was confirmed using PS weighting of Kaplan-Meier survival and CIFs to investigate the average effect of PI strategy on a group level. Patients in the PI group had lower prevalence of diabetes mellitus and were more often previous- or current smokers. Diabetes mellitus is associated with more widespread atherosclerotic- and coronary artery disease, and increased morbidity and mortality in patients with acute coronary syndromes, compared with non-diabetic patients.[34] Smoking has not been associated with increased infarct size or adverse events in pPCI treated STEMI patients, compared with non-smokers.[35]

There is good evidence for treating STEMI patients with a pPCI strategy provided it can be delivered within a timely manner,[1] but time delays to pPCI often exceed what is expected. Studies have documented that a certain proportion of STEMI patients in contemporary clinical practice do not receive pPCI within the recommended time limits, with associated poorer outcomes compared with timely reperfusion.[15 36–38] This study demonstrates improved long-term prognosis with a PI strategy when there are long transfer distances to an invasive centre. Importantly, the PI strategy reduced time to attempted reperfusion with median 120 min compared with the pPCI group. When fibrinolysis was successful, the shorter

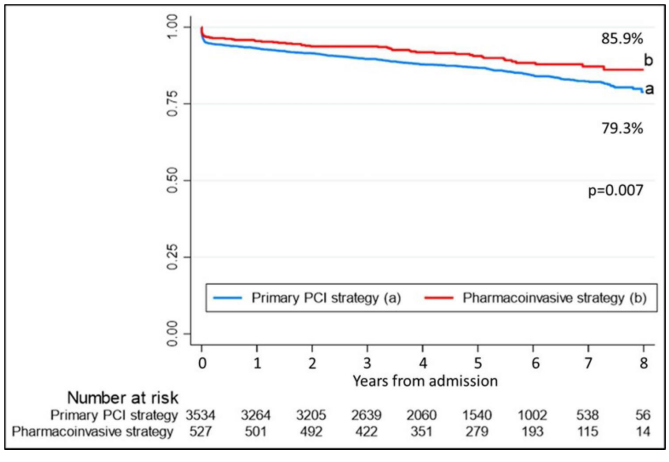

Figure 2 Kaplan-Meier survival estimates. STEMI patients <80 years. Median follow-up 4.7 years (25–75th percentile: 3.0–6.3). PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

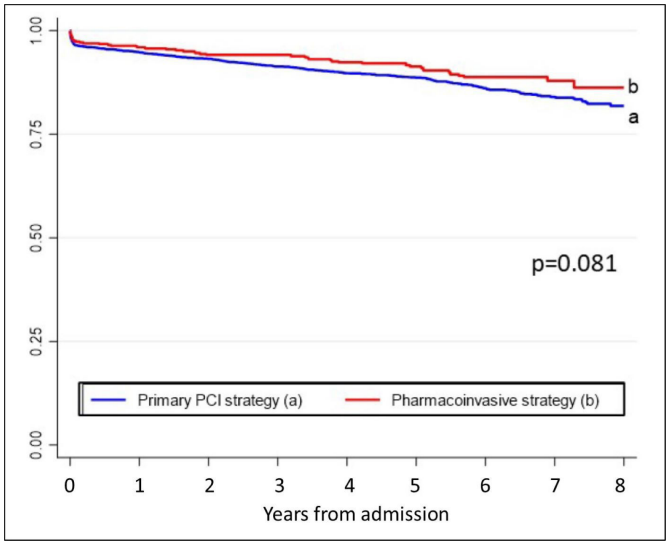

Figure 3 Propensity score weighted Kaplan-Meier plot. Long-term survival in STEMI patients <80 years.PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

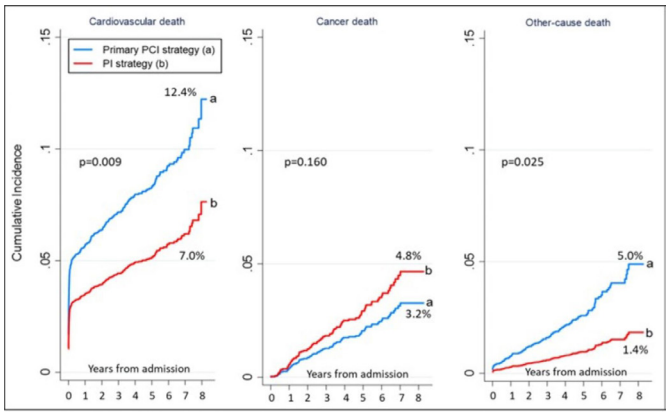

Figure 4 Competing risk analysis. Unadjusted, cumulative incidence function (CIF). Long-term cardiovascular-, cancer- and other cause deaths. STEMI patients <80 years. PCI, percutaneous coronary intervention; PI, pharmacoinvasive; STEMI, ST-elevation myocardial infarction.

time to reperfusion may have contributed to myocardial salvage and smaller infarcts.[39]

The effect of a PI versus pPCI strategy for STEMI patients is still debated, as several RCTs comparing the two strategies have been neutral. The earlier Comparison of Angioplasty and Pre-hospital Thrombolysis In acute Myocardial Infarction trial compared primary angioplasty and fibrinolysis, with no difference in 30-day mortality, but with lower 5-year mortality for the fibrinolysis-group if treated within 120 min.[40] The Strategic Reperfusion Early after Myocardial Infarction study, compared a PI strategy with pPCI in patients who could not undergo pPCI within 60 min, and was neutral with respect to mortality.[30] Some observational studies report no significant difference in all-cause death or composite of ischaemic or bleeding outcomes for up to 1 year, comparing a PI strategy with pPCI.[41–43] To our knowledge, our study presents the longest survival data for STEMI patients with contemporary treatment, stratified by reperfusion strategy. We document an 8-year survival of 85.9% in the PI group and 79.3% in the pPCI group. This is in line with results from Danchin *et al* reporting a 5-year survival for STEMI treated with a PI strategy of 89.8% vs 88.2% in patients treated with timely pPCI (ie, ≤120 min from diagnostic ECG) and 79.5% in patients treated with late pPCI (>120 min from diagnosis).[8] After adjustment, 5-year mortality risk was increased in patients treated with late pPCI compared with a PI strategy. Recently, Jortveit *et al* published similar results from a Norwegian nationwide registry including over 21 000 STEMI patients, comparing a PI strategy with timely, delayed or late pPCI. Importantly, only 54% received timely pPCI (within 120 min from first medical contact (FMC)). Patients treated with delayed (120–180 min from FMC) or late pPCI (>180 min from FMC) had increased risk of long-term mortality, when compared with a PI strategy.[38]

These recent studies highlight that timely reperfusion is still a challenge in contemporary treatment of STEMI patients, with risk of a poorer survival if delayed. There is a need for more knowledge about prognosis after treatment in everyday clinical practice with systematic application of a PI strategy based on geographical distance and estimated time to pPCI >120 min. Bearing in mind that STEMI patients in many areas of Europe do not receive any reperfusion at all,[14] and that only 25%–30% of hospitals in the US perform PCI around the clock,[43] our results should encourage establishment of regional systems for prehospital STEMI diagnosis and fibrinolytic treatment. Such systems could enable increased use of a PI strategy for eligible STEMI patients with long transfer distances to PCI. Future studies should aim to document real-life pPCI related time-delays and the proportion of patients experiencing successful fibrinolysis, to possibly change systems of care and achieve timely reperfusion rates.

Strengths and limitations

The strengths of this observational study were almost complete prospectively collected data for a large clinical population, treated in an established regional STEMI network providing fibrinolysis in case of long transfer distances to PCI. The study population is well characterised, without loss to follow-up, yielding results with high internal validity. The results indicate a superior long-term prognosis for STEMI patients treated with a PI strategy and reflect the treatment effect in an organised network allocating patients to the most efficient reperfusion strategy. Even with the use of advanced statistical methods, we cannot rule out residual confounding in our analyses due to selection bias in the choice of treatment. Possible sources for selection bias might be recent surgery, previous major bleeding, use of oral anticoagulants or non-cardiac comorbidities, representing contraindications to fibrinolysis and thus resulting in the choice of a pPCI strategy. The time of symptom onset was registered, but not the time of STEMI diagnosis; thus time from symptom onset to diagnosis could not be calculated. Information about left ventricular ejection fraction (EF) would have been of interest and could possibly be an effect modifier of the exposure–outcome association, but information about EF was unavailable in the Ullevaal MI registry. Only patients who survived until admission at OUH Ulleval were included by study design, which generally will create a potential for immortal time bias.[44] However, because of relatively short transfer delays and that there is no knowledge of a higher risk of prehospital death with either reperfusion strategy, we believe this is not a concern. Due to the observational design of this study, inference of short-term and long-term mortality with either treatment strategy should be limited to similar hospital-admitted STEMI cohorts, treated in corresponding regional systems with prehospital diagnosis and PI treatment based on estimated transportation delays to PCI. Patients were treated during 2005–2011, before the widespread use of drug eluting stents, radial access coronary angiography and modern P2Y2 inhibitors such as ticagrelor and prasugrel. Thus, new studies should document the short- and long-term prognosis for STEMI

patients with either reperfusion strategy with these improvements related to PCI and antiplatelet drugs.

CONCLUSIONS

Patients with STEMI aged <80 years treated with a PI strategy had similar 30-day mortality and better 8-year survival compared with pPCI treated patients in our established regional STEMI network. Risk of long-term mortality and CV death was lower in the PI group also after adjustment. These findings support the use of a PI strategy in STEMI patients without contraindications to fibrinolysis, when pPCI cannot be performed within 120 min from diagnosis.

Impact on daily practice

A significant proportion of STEMI patients in remote areas cannot receive pPCI within 120 min from diagnosis. This study adds to evidence that STEMI patients <80 years treated with a PI strategy experienced a better long-term prognosis compared with pPCI-treated patients. Systems of care should be established with the possibility to use a PI strategy in areas with long transportation distances to an invasive centre.

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Patient consent for publication Not applicable.

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